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14. ABSTRACT

In the proposed study, magnetoencephalography (MEG) is used to measure brain activity during auditory and language-specific processing in nonverbal children with ASD, verbal children with ASD, and healthy comparison children. The proposed project will address the challenges involved in imaging nonverbal children by: a) assessing function that does not necessitate a verbal response, b) including multiple pre-imaging training methods to increase participant comfort and cooperation, and c) applying motion correction techniques post-recording to minimize movement artifacts. In addition, behavioral language measures will be collected to validate these neural markers as measures of language function. Thus far, we have consented and collected imaging and behavioral data from 15 participants (9 ASD minimally verbal, 6 ASD verbal) and are expanding our recruitment efforts through a recently approved no-cost extension into a third year. Thus far, the combination of motion-correcting technology and positive behavior supports (via a multimedia participant orientation kit) has resulted in improved data quality for difficult-to-image children.

15. SUBJECT TERMS
Autism spectrum disorders, magnetoencephalography (MEG), neural biomarkers, nonverbal

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1. Introduction

Nonverbal individuals with autism spectrum disorders (ASD) are currently underrepresented in neuroimaging studies of ASD, leaving a critical gap in the understanding of language processing in ASD. The proposed project aims to address this gap by investigating auditory and language-specific processing in nonverbal children with ASD, in comparison to verbal children with ASD and typically developing healthy comparison children.

Language and communication deficits are core symptoms of autism spectrum disorders and as many as a quarter of individuals with ASD are estimated to lack functional verbal skills[1]. The neural mechanisms involved in ASD are still largely unknown and even less is known for those who are minimally verbal. Determining points of processing at which deficits may lead to a lack of speech is critical for understanding language impairment in ASD. Assessing language comprehension in nonverbal children is challenging due to expressive language impairments; that is, given that this population has very low output of language, it is difficult to determine their level of verbal understanding. As such, the identification of biomarkers of language function that can be measured without a verbal response will be an important asset for evaluation of deficits and treatment outcome in this population.

In this project, magnetoencephalography (MEG) is being utilized to measure brain activity during auditory and language processing in 3 groups: 1) nonverbal children with ASD, 2) verbal children with ASD, and 3) healthy comparison children. During MEG recording, participants complete two passive tasks not requiring a response. The first is a simple 5-minute auditory task during which participants hear a series of white noise stimuli[2, 3]. The second is a 15-minute language task (with brief breaks throughout), in which participants hear spoken words followed by pictures that either match (e.g., spoken word "lion", picture of a lion) or do not match (e.g., spoken word "lion", picture of a boat). Brain activity recorded during these tasks will provide three measures that have been implicated as biomarkers in ASD[2-4]: synchronized brain activity in the gamma frequency range (30-80 Hz), the M100 evoked field, and the M400 evoked field. The working hypothesis is that nonverbal children with ASD will show exaggerated deficits compared to those previously found in verbal children with ASD. This project has the potential to contribute to the knowledge of underlying neurophysiology in language processing in ASD, as well as identifying a more effective measure of language comprehension in nonverbal children with ASD.

2. Keywords: autism, neuroimaging, minimally verbal, auditory processing, language processing, biomarker

3. Accomplishments

The accomplishments of the project are described below with respect to the Scope of Work for Year 2 (Sept 1,2014 – August 31, 2015).

SOW: Task 3. Participant Recruitment/Enrollment, Months 1-22
a. Coordinate recruitment strategy
b. Send out recruitment letters to patient database and various agencies such as local community centered boards, especially Developmental Pathways.
c. The PRA will conduct eligibility screening and informed consent process.
d. When ADOS/ADI-R information are not available for participants in autism groups, qualifiying interviews for qualifications are conducted by Dr. Hepburn and/or her staff.
e. For eligible participants, videos and MEG brochure will be sent to parents to familiarize participants with MEG procedures.

Progress: Each of these steps was accomplished in Year 2. Recruitment efforts were enhanced through the provision of community education offerings for parents of children with ASD and outreach to clinicians at Children's Hospital Colorado. During Year 2, 32 participants were screened for study eligibility; 18 met eligibility criteria and 15 consented to participate in the MEG study. Recruitment is ongoing.

SOW: Task 4. MEG Scans and Behavioral Assessments, Months 2-22
a. MEG training (1 lab visit, if needed)
b. MEG scans during auditory and language tasks (1 lab visit)
c. Behavioral assessments (1-2 lab visits over 2 month period)

Progress: Fifteen study participants initiated study involvement in Year 2. Thus far, 12 have completed the behavioral battery and 3 are in process; 9 have completed the MEG scans and 6 are in process. The "in process MEG" group represents youth who require a gradual desensitization to the imaging equipment.
Of the 9 individuals who completed the MEG scans, 6 are minimally verbal and 3 are verbally fluent. Thus far, motion correction procedures and behavioral coaching have been effective in maximizing data collection from individuals with significant impairments in communication and behavior.

SOW: Task 5. Interim Analyses, Months 10-16
a. Interim statistical analyses of data obtained from MEG and behavioral/cognitive assessments. This will be done as each outcome measure reaches a minimum of 8 completed participants per group.
b. Annual reports will be written.

Progress: Interim analyses are pending, given that we have not yet imaged a sufficient number of children with ASD from both groups. We anticipate completing this analysis in October of 2015. Preliminary examination of the feasibility of engaging minimally verbal youth in the imaging tasks was completed by Isabelle Buard, Ph.D. and Kristina McFadden, Ph.D. early in Year 2. The results of those analyses supported the utility of the brief passive listening task for individuals with self-regulation challenges.

SOW: Task 6. Final Analyses and Report Writing, Months 18-24
a. Final analyses of data from behavioral and MEG experiments will be performed.
b. A final report and initial manuscripts will be prepared for submission to peer-reviewed journals. It is anticipated that between 1-2 manuscripts will be generated by this research project.

Progress: We have not accomplished this task, as we need to collect more data from participants in both groups in order to analyze effectively. We submitted a request for a No-Cost Extension in order to spend more time recruiting, enrolling and collecting behavioral and imaging data from participants. Thankfully, we received approval to extend our data collection for several more months and we now plan to begin addressing this task in the summer of 2016.

4. Impact

There are two primary ways that this study will impact research and practice:
(1) Identify strategies and develop tools for engaging minimally verbal individuals with ASD in neuroimaging research: Neuroimaging in this population is challenging due to communication difficulties (both in comprehension and expression), apprehension and/or anxiety (i.e., the technology is unfamiliar and constraining movement can be distressing) and self-regulation demands of remaining still during imaging. Currently, it is common to use anesthesia or sedation when neuroimaging is recommended in this population, which has many health risks. The proposed project aims to tackle these challenges by developing a multi-media participant orientation kit, with explicit pre-imaging training and procedural guides tailored towards supporting nonverbal individuals with ASD through a neuroimaging protocol. Specifically, we have created a short film that illustrates the imaging process, which we mail to prospective participants, along with a social story and a pictorial representation of the study steps. (We will attach these in the Appendix.)

We are continuing to revise these tools and are obtaining feedback from parents, educators and persons with ASD in an effort to create a functional, easy-to-implement and easy-to-disseminate tool kit for other scientists or physicians to use in research or clinical contexts. It is our hope that the tools created in this project will provide a feasible alternative to sedation when neuroimaging of a minimally verbal person is required. In

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addition, publication of research detailing successful methods for neuroimaging in this population may encourage the inclusion of this underrepresented group in future neuroimaging research studies.

(2) Increase knowledge of the underlying neurophysiology in autism during language processing: The underrepresentation of nonverbal individuals in neuroimaging research of ASD leads to a lack of knowledge regarding brain function in this population. To fully understand the causes of language impairment in nonverbal individuals, it is critical to include them in studies that investigate the underlying neurophysiology of this impairment. Among children with ASD, there are a number of potential factors contributing to language impairment, including cognitive impairment, speech-motor difficulties, deficits in auditory processing, and impaired semantic processing. Previous studies have found evidence suggesting language deficits in ASD may result from impairments at a sensory encoding level, as seen by abnormal brain activity during auditory processing. Other studies suggest deficits are language-specific and involve higher-order cognitive processes. These hypotheses are not mutually exclusive, as impairments in processing at both early sensory and later cognitive stages may underlie language impairments in ASD. Determining points of processing at which deficits lead to a lack of speech is critical for understanding language impairment in ASD and for developing targeted treatments at an individual level.

5. Changes/Problems

Just prior to beginning Year 2 of this project, the original PI (Kristina McFadden, Ph.D.) received notification that she'd been awarded a K award from NIH, which provides five years of support and enriched professional development opportunities, under the agreement that the grantee focuses his or her work entirely on the activities of the K award. Thus, Dr. McFadden worked with administrators at the University of Colorado and Department of Defense in order to obtain approval to transfer the role of PI to Susan Hepburn, Ph.D. (Co-Investigator on this project and Mentor to Dr. McFadden in her post-doctoral projects focused on ASD). Dr. Hepburn assumed the role of PI in September of 2014. Study activities were put on hold until the Colorado Institutional Review Board and the Department of Defense Human Subjects Review Board approved the modifications to study personnel and procedures. An administrative error on Dr. Hepburn's part contributed to an extended delay in obtaining COMIRB approval to approve the personnel plan; thus the team was not able to meet the enrollment/data collection goals for Year 2. The team sought and was approved for a No-cost extension period of one year, which will enable them to increase recruitment, enrollment and data collection and meet their analytical goals by the summer of 2016.

6. Products

The activities of this grant have resulted in three products designed to support minimally verbal persons in neuroimaging studies: (a) short film of an imaging visit; (b) social story; (c) visual supports for use during the appointment. These products are used in the study and another round of feedback from participants is being sought to finalize them. (See Appendix for draft versions of these tools).

Scientifically, data are still being collected and analyzed. Three manuscripts are planned for submission to a peer-reviewed journal. These are: (1) *Assessing the validity of specific neural markers as measures of language function in youth with ASD*; (2) *Neural markers of language impairment in minimally verbal youth with ASD, relative to verbal youth with ASD and typically developing children*; and (3) *Improving data quality in MEG studies of minimally verbal children with ASD: Integrating motion correction technology with positive behavior supports*

7. Participants & Other Collaborating Organizations

The following personnel committed more than 1.0 months during Year 2 of this project:

Susan Hepburn, Ph.D.	Role = PI	1.44 calendar months
Isabelle Buard, Ph.D.	Role = Co-I, Technician	1.20 calendar months
Lisa Ankeny, M.S/	Graduate Assistant	2.40 calendar months
Caren Rhodes, M.Ed.	Graduate Assistant	2.40 calendar months

In-kind consultation was provided by Donald Rojas, Ph.D., a colleague and collaborator of Dr. Hepburn's and Dr. McFadden's (original PI). Dr. Rojas meets with Dr. Hepburn regularly to review the neuroimaging aspects of the study. Dr. McFadden continues to participate in scientific discussions concerning the project and will be included in the analysis and manuscript preparation phases of the project (assuming approval from her K-award committee).

Two non-profit educational/day programs serving persons with ASD in the greater Denver community (Joshua School, Temple Grandin School) have collaborated with the research team to generate awareness of the study and to reach families of minimally verbal youth.

Members of the Parent/Family Faculty of the Leadership Education in Neurodevelopmental Disorders (LEND) Program at JFK Partners (University Center for Excellence in Developmental Disabilities; Kristen Kaiser, Jill Pidcock) have provided feedback on the participant orientation kit and have consulted with the team on the wording of consent forms and flyers.

8. Special Reporting Requirements

n/a

9. Appendices
1. MEG Story from the Participant Orientation Kit

MEG Picture Story (Note: We present this story to the participants as a scrollable pdf with voicover (optional) on a portable USB. They receive this story and information sheets and a short film about the MEG appointment).


David is going to meet with a scientist who studies the human brain.

The scientist uses a machine called an "MEG" to measure brain activity.

This is the room where the MEG machine is. The machine is very powerful. Just like an x-ray machine, its okay to be near the machine when its working sometimes, but not all the time. That's why the room has large doors that shut tightly.

If David decides to do the study, he will only be in the room for a short time – about as long as an episode of his favorite show – The Big Bang Theory.
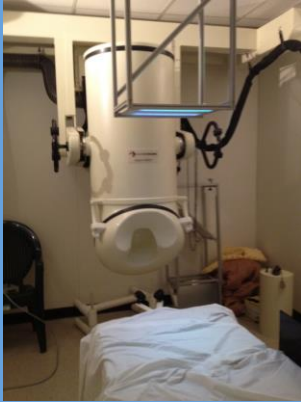
This is what the machine looks like inside the room. A person lays down on the table and the scientist gently lowers the machine so that it is sitting above the person's head. The person's body is outside of the machine.

David sits on the table and looks at the machine. It's smooth, cold and clean. Right now, it's quiet, but when the scientist turns it on, it will make a humming and knocking sound. The sounds are not loud, but they keep going for several minutes at a time. It sounds like air being pumped into a tire.

David lays down. He looks up and can see a computer screen showing clips from the movie "Avatar". The scientist gave him a choice of 3 different movies. He liked "Avatar" best.

The scientist rolls David's table under the MEG machine. He is still watching "Avatar". The scientist is getting the machine's sensors ready – these are small sticky pieces of plastic that will be placed on David's face and head. Then, they will connect to the MEG machine. Sensors do not hurt. They feel like putting on a bandaid.

The scientist gently puts the sensors on David's head. This takes a few seconds for each sensor. There are about 10 sensors.

The scientist gently brings the machine closer to David. She guides his head so that it is resting comfortably. David stays still and the scientist moves the machine so that it is at the correct angle. Everything is quiet – except for the Avatar movie.

This is what it looks like when the machine is in the correct position. It works like a helmet. To David, it just feels like he is wearing a big hat that gently touches his face and goes all the way to the ceiling. It is still quiet.

The scientist asks David if he is comfortable. Then, she asks him to stay still for about 5 minutes. She's going to leave the room and turn on some sounds. She wants him to listen and try not to move. He doesn't have to do anything else.

Five minutes later, the scientist comes back and moves the machine back and away from David's head.

David makes a joke that he took a little nap.

The scientist thanks him for being so still and resting like he did.

The scientist gently takes the sensors off of David's head. It doesn't hurt at all.

David is all done with the MEG study!

The scientist thanks him for his time and gives him a Gift card to spend later.

David has helped the scientist and is ready to go home.

Thanks David!